

SOME ANALOGUES OF SULFANILAMIDE

BY

ALVA JOSEPH JOHANSON

A.B., Brigham Young University, 1931

M.A., Brigham Young University, 1934

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN
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INTRODUCTION AND HISTORICAL

In 1935, Domagk¹ announced the remarkable activity of 2,4-di-aminoazobenzene-4'-sulfonamide (prontosil) as a therapeutic agent in the treatment of experimental streptococcal infections in mice. His observations were soon confirmed by other workers^{2,3,4,5,6}. It was later shown that the activity of this substance is due to the *p*-aminobenzenesulfonamide (sulfanilamide) portion of the molecule⁷, and that in the infected animal, prontosil is converted into sulfanilamide⁸. Sulfanilamide, as such, has proved to be as effective as prontosil, and is coming rapidly into widespread clinical use. In addition to β -hemolytic streptococcus, many other types of infections have been found susceptible to its action.

Sulfanilamide possesses two disadvantages, first, its low water-solubility which makes parenteral injection impracticable and, second, its toxicity which often leads to serious physiological disturbances when the compound is used clinically.

It was the purpose of this work to synthesize a number of analogues or derivatives of sulfanilamide in which, it was hoped, these disadvantages might be overcome without destroying the activity and which might possibly have greater activity than sulfanilamide.

EXPERIMENTAL AND DISCUSSION

Sulfanilamide is prepared by the method of Gelmo⁹. *p*-Acetaminobenzenesulfonyl chloride is condensed with an excess of aqueous ammonia and the acetyl group removed from the resulting compound by means of acid hydrolysis.

The following series of sulfanilamide analogues were prepared by adaptations of this method.

1. *Alkanol Analogues of p-Acetaminobenzenesulfonamide.* *p*-Acetaminobenzenesulfonyl chloride, prepared by the action of chlorosulfonic acid on acetanilide¹⁰, was condensed with equimolar portions of the following alkanolamines and related amino compounds: monoethanolamine, diethanolamine, *n*-propanolamine, isopropanolamine, isobutanolamine, α -glycerolamine, 1,2-

sulfonyl chloride with ethanolamine and isopropanolamine.

6. *Morpholine Analogues of Sulfanilamide.* *p*-Acetaminobenzenesulfonyl chloride was condensed with morpholine. A portion of the product was hydrolyzed to remove the acetyl group. The *p*-propionamino-, *p*-butyramino-, *p*-isobutyramino- and *p*-carbethoxyaminobenzenesulfonyl chlorides were also condensed with morpholine to form the corresponding morpholides. An additional one to one and one-half moles of morpholine was used as the condensing agent in each case.

7. *Derivatives of 4-Methoxy-3-Aminobenzenesulfonamide.* 4-Methoxy-3-acetaminobenzenesulfonyl chloride¹¹ was condensed with ammonia, ethanolamine, isopropanolamine and isobutanolamine, using potassium hydroxide as the condensing agent in the last three cases. In the first and third examples the free amine was also produced by hydrolytic removal of the acetyl group.

8. *Derivatives of Di-Sulfanilamide* ($\text{NH}_2\text{C}_6\text{H}_4\text{SO}_2\text{NHC}_6\text{H}_4\text{SO}_2\text{NH}_2$). *p*-Acetaminobenzenesulfonyl chloride was condensed with the isopropanol and isobutanol analogues of sulfanilamide to produce the corresponding acetyl di-sulfanilamide derivatives. Excess pyridine was used as the condensing agent. Portions were hydrolyzed to the free amines. *p*-Carbethoxyamino- and *p*-butyraminobenzenesulfonyl chlorides were also condensed with the isopropanol derivative of sulfanilamide.

All of the compounds prepared are white crystalline solids. The *p*-amino- and *p*-acetaminobenzenesulfonalkanolamides proved to be more water-soluble than sulfanilamide. The remaining compounds are, with few exceptions, less soluble than sulfanilamide.

The compounds were tested for anti-streptococcal and anti-meningococcal activity in experimentally infected mice, through the courtesy of Dr. Perrin H. Long and Dr. Eleanor A. Bliss at the Johns Hopkins University, Medical School, Baltimore, Md. Many of them were found to be active toward streptococcus but in no case is the activity equal to that of sulfanilamide. In general, the compounds are much more active toward meningo-

coccus, several of them being equal to sulfanilamide in this respect.

These analogues are generally less toxic than sulfanilamide in experimental animals.

Their therapeutic value in clinical practice has not been determined.

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VITA

The writer was born at Rexburg, Idaho, on May 10, 1903. He received his early education in the public schools of Rexburg and vicinity and was graduated from high school in 1921. He attended Ricks Junior College at Rexburg, from 1921 to 1923. During the period from 1923 to 1929 he was employed for three years as a teacher in the public schools of Fremont and Jefferson Counties, Idaho.

He entered Brigham Young University, Provo, Utah, in September, 1929, and was graduated from that institution, with honors, in June, 1931. He served as an assistant in chemistry at Brigham Young University from 1931 to 1934, receiving the Master of Arts degree in June of the latter year. During the following two years he was employed as instructor in chemistry, and now holds the position of assistant professor of chemistry at that institution.

He entered the Graduate School of the University of Illinois in 1936 where he held a teaching assistantship in chemistry during the school year 1937-38.



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